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Original Communication

Interpretation of lesions of the cardiac conduction system in cocaine-related fatalities

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Abstract

This study examines cases of chronic drug users who died suddenly after drug administration. Victims were young subjects, aged from 19 to 35 from Switzerland and known to the police as long-term drug users. The circumstances of death suggested the occurrence of a sudden, unexpected death. Some victims were undergoing methadone treatment. In each case, a forensic autopsy and toxicological analyses were performed at the Institute of Forensic Medicine in Lausanne in Switzerland between 2002 and 2004, including hair analysis as a means to establish chronic drug use in general, and cocaine use in particular. The conduction system was examined histologically and cases showing potentially lethal changes were chosen for this report. The most frequent lesions found were severe thickening of the atrioventricular node artery, intranodal and perinodal fibrosis, and microscopic foci of chronic inflammatory infiltration. The authors conclude that pathological lesions in the conduction tissue may play a role in the occurrence of death attributed to intoxication consecutive to cocaine ingestion.
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Keywords: Cocaine; Cardiac conduction system; Hair drug testing; Drug abuse

1. Introduction

In times of budgetary constraints and in cases of death of drug addicts, the examining magistrate may be tempted to limit the forensic investigation to an external examination of the corpse and toxicological analyses. The forensic scientist will invariably advise the magistrate against such a simplification. Why would the scientist advise this? To answer this question, the forensic scientist should explain that post-mortem toxicological analyses might only be correctly interpreted after a complete autopsy and exclusion of any other cause of death. He or she might add that because chronic drug addicts use habit-forming substances, their levels in the blood may be very high, without any overt clinical signs. In our practice, a discussion with the magistrate is followed by an autopsy and then by toxicological analysis. In some cases, the autopsy itself or microscopic examinations reveal a pathological lesion that explains death. In other cases, the toxicological analysis may be required to determine cause of death. Such analysis requires appropriate interpretation. One of the first facts that need to be established is whether the victim was indeed a systematic abuser of the one or many substances found in the blood. Hair analysis will answer this question and the levels found for the victim can easily be compared with data available in the literature. However, what does one conclude if the victim's hair tests positive but his or her blood levels turn out relatively low? Could such a case be considered as intoxication? Could there be an alternative explanation, such as a sudden death in a young adult? Because lesions in the conduction system sometimes explain sudden death, especially in young subjects, the conduction tissue must be analysed. This examination is also

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useful because the cardiac toxicity of drugs in general, and of cocaine in particular, may result in early myocardial fibrosis, foci in the myocardium and accelerated atherosclerosis.[1–13] Such lesions may constitute the morphological substrate for arrhythmia and lead to fainting and even explain sudden death. At the same time, a survey of the literature shows that the conduction system is very rarely examined in drug addicts, in particular in victims whose chronic consumption is confirmed by hair analysis.[9] It is thus of interest to present and discuss cases of chronic cocaine users presenting specific lesions in the conduction system.

2. Materials and methods

2.1. Cases

Selected were six cases of chronic cocaine abusers with pathological findings detected during cardiac conduction system examination. The circumstances of death suggested the occurrence of a sudden, unexpected death. All victims were young individuals from Switzerland, aged 19–35, known to the police as long-standing drug addicts. Almost all victims were undergoing methadone treatment. In each case, a complete autopsy and toxicological analyses were conducted at the Institute of Forensic Medicine in Lausanne in Switzerland, between 2002 and 2004. Hair analyses were positive for cocaine for all victims. In several cases, additional substances were also found, such as methadone and opiates.

3. Examination of the heart and of the conduction system

The examination of the heart included macroscopic and histological examinations of at least five slides made from the working myocardium. The conduction system was analysed using a simplified method.[14] Samples of the conduction system were collected from the left approach to the ventricular septum by performing two cuts perpendicular to the aortic valve, one passing through the right coronary artery ostium and the second one through the margin of the attachment of the non-coronary cusp of the aortic valve. The initial block was cut into 6–7 blocks about 2–3 mm wide. At least two histological sections were prepared from each block. The sections were stained with hematoxylin–eosin and with Masson trichrome. Whenever lesions were found, additional sections were prepared.

3.1. Toxicological analyses

Toxicological analyses were performed by GC/MS on samples from femoral vein collected before autopsy. The presence of common abuse substances was assessed, including cocaine and its metabolites, and the results were compared to the published data.[15] In each case, hair analysis was conducted to establish chronic use of cocaine, methadone, opiates, amphetamines and their metabolites.

3.1.1. Cases

3.1.1.1. Case 1. A 35-year-old-man was found dead at home. He was known for cocaine abuse but had no medical records. Forensic autopsy was performed the next day. The heart weighed 390 g and appeared macroscopically normal, the coronary arteries being free of any sign of arteriosclerosis.[16] Only non-specific signs were noticed: visceral congestion and pulmonary edema. The examination of the atrioventricular part of the conduction system of the heart showed some inflammatory cells in the atrioventricular node with no myocyte damage (Fig. 1) and a moderate thickening of a small coronary artery supplying the node. Other organs were normal.

The toxicological analyses of blood samples revealed the presence of opiates and cocaine with a potentially lethal level according to published data.[15] Both groups of substances were also detected in hair.

3.1.1.2. Case 2. The second case concerned a 19-old-yearman. He was found dead and according to police investigations, the day before he had sniffed cocaine and had complained about not feeling well. He was under methadone treatment.

The autopsy was performed 2 days later. Pulmonary edema and visceral congestion were noticed. The heart was macroscopically normal and weighed 320 g.[17] No pathological lesions were found. Histological examination of the myocardium showed multiples foci of chronic myocarditis involving also the left bundle branch (Fig. 2). In the lateral wall of the left ventricle, small patches of fibrosis and contraction band necrosis were also noticed. On microscopical examination, the other organs were normal.

Toxicological analyses revealed the presence of benzodiazepines in the blood. The blood concentration of benzoylecgonine was low, below the lethal level. No alcohol was detected. Hair analysis confirmed chronic use of cocaine and methadone.

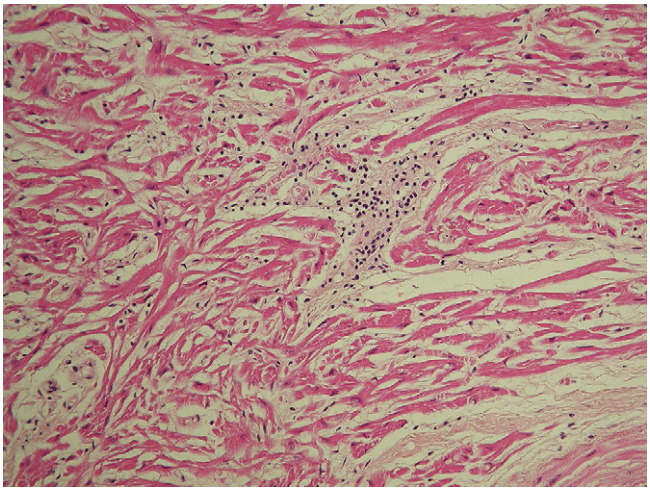

Fig. 1. Chronic inflammatory cells in the atrioventricular node (case 1), hematoxylin–eosin stain.

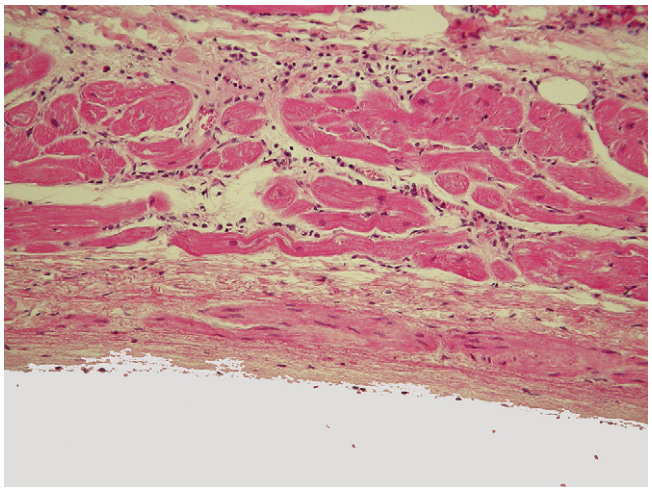

Fig. 2. Myocarditis involving the left bundle branch (case 2) hematoxylin–eosin stain.

3.1.1.3. Case 3. A 22-year-old-man collapsed at home in the presence of his family. He was under methadone treatment.

The heart weighed 330 g and appeared macroscopically normal. In the myocardium of the superior septum, fibrous patches were found. A fibromuscular dysplasia of an artery supplying the bundle of His was also noticed with an important thickening of the wall (Fig. 3).

The toxicological analyses performed on the blood samples revealed a potentially lethal level of opiates and methadone, and "normal" concentrations of phenobarbital and sertraline. Traces of cocaine and of its metabolites were detected in the urine. Hair analysis indicated chronic abuse of opiates, methadone and cocaine.

3.1.1.4. Case 4. A 23-year-old-man, known by the police as a drug user and undergoing methadone treatment, was found dead at home by his ex-girlfriend.

The autopsy revealed non-specific signs such as visceral congestion and pulmonary edema. The heart was macroscopically normal and weighed 340 g. The histological examination was normal with the exception of an important thickening of small arteries and fibrous scars of the myocardium seen on the slides from the septum superior. Fibrosis was observed in the bundle of His (Fig. 4).

Toxicological analyses revealed the presence of methadone at a concentration, which could be considered both as potentially lethal but also as "normal". Low concentrations of nordiazepam and of benzoylecgonine were also measured. Blood ethanol concentration was 0.17 gram per kg. Cocaine metabolites were detected in the urine. Hair examination indicated chronic use of cocaine and methadone.

3.1.1.5. Case 5. A 32-year-man was found dead at home. He suffered from schizophrenia and had left the psychiatric hospital a few days before his death. He was known to take cocaine by injection.

During the autopsy, numerous needle marks were noticed on the forearms and legs. Internal examination revealed only signs of pulmonary edema and visceral congestion. The heart weighed 340 g and was macroscopically normal.

The microscopical examination of the heart showed an important thickening of an artery in the atrioventricular node (Fig. 5) and small fibrous patches in the myocardium.

The toxicological analyses of the blood samples revealed a relatively low concentration of cocaine. Methadone concentrations were measured at "normal" levels, but which can also be considered lethal. A low blood concentration of sertraline was measured. Hair analysis indicated chronic use of cocaine and methadone.

3.1.1.6. Case 6. A 33-year-old-man was found dead at the bottom of the stairwell of his home. He was known as an ancient drug abuser. According to his girlfriend, he had

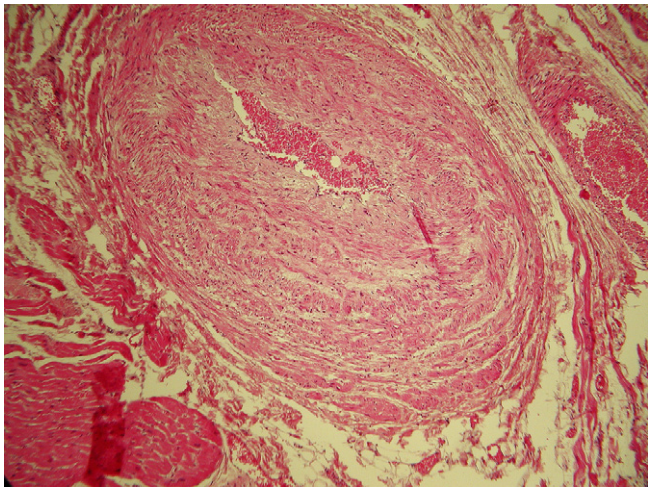

Fig. 3. Fibromuscular dysplasia in the superior septum (case 3) hematoxylin–eosin stain.

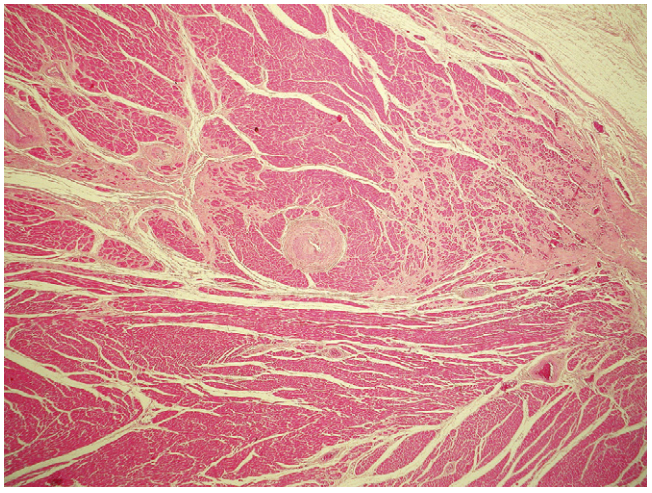

Fig. 4. Thickening of small intramural arteries (case 4) hematoxylin–eosin stain.

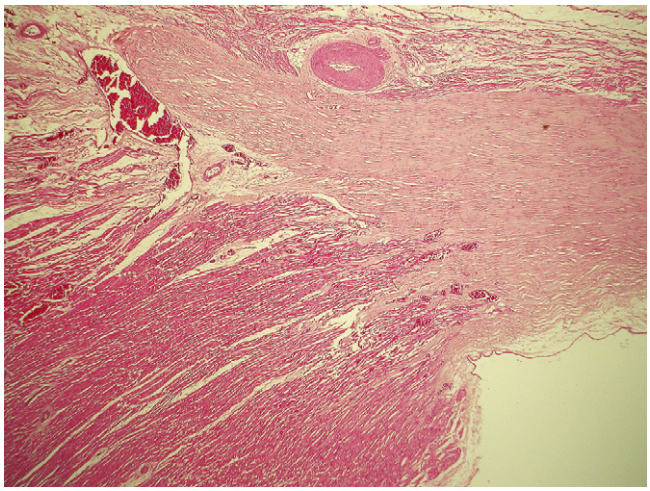

Fig. 5. Thickening of an artery in the atrioventricular node (case 5) hematoxylin–eosin stain.

started abusing substances again a week prior to his death and to inject cocaine.

During external examination, numerous needle marks were noticed on the forearms. At autopsy, a visceral congestion and pulmonary edema were observed. The heart weighed 400 g. No macroscopic lesions were found. The histological examination of the liver showed signs of persistent chronic hepatitis.

A loss of an important part of conduction fibres was observed in the origin of the left branch and an important fatty infiltration could be seen in the distal part of the left bundle branch (Fig. 6).

The toxicological analyses of the blood samples showed a potentially lethal level of methadone. Cocaine concentrations were below lethal levels. Benzodiazepines and venlafaxine were detected at low concentrations. Hair analysis confirmed the chronic use of cocaine and methadone.

The autopsy findings are summarized in Table 1. The results of toxicological analyses are shown in Table 2.

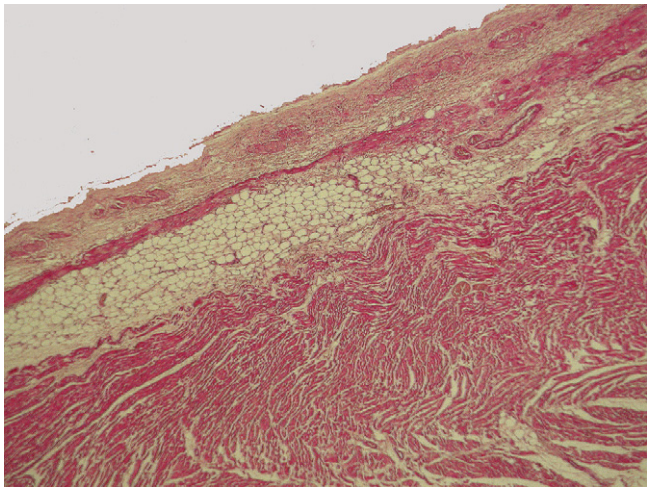

Fig. 6. Fatty infiltration in the distal part of the left bundle branch (case 6) hematoxylin–eosin stain.

Table 1
Summary of the cases and predicted heart weight

	Age	Sex	Body height (cm)	Body weight (kg)	Heart weight (g)	Predicted heart weight (g)	Autopsy findings	Histology of the myocardium and of the cardiac conduction system
Case 1	35	m	182	64	390	312	Visceral congestion, pulmonary edema	Discrete inflammatory infiltration of the atrio-ventricular node Moderate thickening of a small artery supplying the node
Case 2	19	m	170	61	320	246	Visceral congestion, pulmonary edema	Foci of chronic myocarditis involving the left bundle branch
Case 3	22	m	190	75	330	339	Visceral congestion, pulmonary edema	Small fibrous patches in septum Fibromuscular dysplasia of an artery supplying the bundle of His
Case 4	23	m	178	65	340	315	Visceral congestion, pulmonary edema	Small fibrous patches in the septum Thickening of small arteries in myocardium Fibrosis in the bundle of His
Case 5	32	m	178	75	340	339	Visceral congestion, pulmonary edema	Severe thickening of a small artery in the atrio-ventricular node Small fibrous patches in myocardium
Case 6	33	m	175	79	400	347	Visceral congestion, pulmonary edema	Loss of conduction fibres in the origin of the left bundle branch Fatty infiltrations in the distal part of the left bundle branch

Table 2
Summary of the toxicological analyses of the blood and hairs samples (nd; not detected, nm; not measured, BZE; benzoylecgonine)

Case	Ethanol (g/kg)	BZE		Cocaine		Methadone		Morphine		Nordiazepam	
		Blood (mg/L)	Hair (ng/mg)	Blood (mg/L)	Hair (ng/mg)	Blood (mg/L)	Hair (ng/mg)	Blood (mg/L)	Hair (ng/mg)	Blood (mg/L)	Hair (ng/mg)
1	0	nd	3.55	1.46	9.94	nd	nd	0.54	0.20	nd	nm
2	0	0.21	3.09	nd	4.61	0.20	0.65	nd	nd	0.22	nm
3	0	nd	3.21	nd	10.0	1.98	38.2	0.30	3.55	nd	nm
4	0.17	0.15	1.76	nd	3.11	0.39	0.35	nd	nd	0.79	nm
5	0	nd	98.0	0.82	104.0	0.78	32.0	nd	nd	nd	nm
6	0	nd	18.0	0.15	28.8	1.10	45.4	nd	nd	1.30	nm

4. Discussion

In the presented cases, different lesions of the conduction system were identified. Naturally, the first question that must be answered is whether these lesions can explain the occurrence of sudden death. This may indeed be the case since identical lesions have already been designated by a number of authors as the cause of death in studied cases of sudden death.[18,19] In addition, in several studies conducted in the past, specific lesions of the myocardium and of the conduction system were correlated with clinical findings.[19] Nevertheless, the interpretation of lesions observed in the conduction system has been the subject of controversy for a number of years. These pathologies may represent incidental findings, unrelated to the cause of death. Indeed, such findings have been described in cases of sudden death, caused by hanging or gunshot, where heart-related causes are clearly excluded.[20] Theoretically, to effectively argue that a death had an arrhythmogenic cause would require a comparison between ante-mortem and post-mortem data. In the forensic practice, however, ante-mortem data are rarely available since most cases involve young victims with no prior medical history. In our practice, a case with well-documented arrhythmia would be classified as "death from natural causes" and autopsy would not be performed. In the cases presented here, virtually no clinical information was available. It was thus impossible to make any correlation between clinical findings and anatomical and pathological observations. At the same time, it is well known that cocaine can cause arrhythmia. Cardiac arrythymias in cocaine users have been studied by a number of authors, both in cases of acute intoxication and in chronic cocaine addicts.[21–23] Different mechanisms have been proposed to explain the phenomenon after cocaine administration. Certain models are purely functional and thus exclude a morphological substrate. Other explanations rely on a potentially arrhythmogenic pathology: foci in the myocardium, fibrosis, and thickening of the small arteries. Such lesions have been described in the myocardium of cocaine addicts. Virmani found that 20% of cocaine users suffered from toxic myocarditis.[13] However, the percentage of myocarditis in drug abusers may be higher considering recent publications showing that Dallas criteria are no longer adequate because they are not enough sensible to identify the population with viral or autoimmune-related heart compromise[24–26] Karch, as well as Kloner, have described the presence in the myocardium of small fibrous and the thickening of small intramural arteries.[4–6] In these cases, the same lesions were present at the level of the atrioventricular junction. Although no definite proof is possible, we thus nevertheless believe that the lesions of the conduction system found in cocaine users may be considered as a possible cause for arrhythmia and even death.

Because methadone was present in most cases, one must ask whether administering this substance could have caused possible arrhythmia and perhaps death itself. In

the recent years, researches have observed a change in the QT interval following intravenous administration of methadone, although some authors believe that the QT interval prolongation has no clinical significance.[27,28] The methadone-induced change is clearly functional with no identifiable morphological substrate that could be detected during autopsy. It should be noted however, that QT interval prolongation has been described after cocaine administration as well. Recently, Krantz et al.[22,29] have studied the effects of cocaine and methadone on cardiac conduction in a population of chronic substance abusers. In this work, a temporal relationship was established between arrhythmia and cocaine administration, but not methadone administration.

Another question needs to be addressed: are the described lesions a consequence of cocaine administration? In our practice, we have observed that fibrosis of the conduction tissue appears earlier in cocaine addicts than in the control group. Previous studies on the myocardium of cocaine users also seem to indicate that chronic cocaine use results in pathologic lesions in the conduction system. However, because the same subjects were also chronic users of methadone, the possible effects of this substance on the myocardium must also be considered. A survey of the literature shows that compared to the known cardiotoxicity of cocaine, the effects of methadone on the myocardium are clearly much less severe.[27] Another fact must be taken into account: based on our experience, methadone substitution is also practiced by drug addicts with a know history of cocaine abuse.

One final problem, known to all forensic scientists, is the interpretation of the results of toxicological analyses. In each one of the cases presented here, different substances were detected in the blood and the urine. However, the same substances were detected in the hair of the victims. This finding corroborates the chronic nature of the abuse and suggests increased tolerance. The results of the toxicological analyses indicate that in four cases, the concentrations of methadone reached levels that can be considered potentially lethal.[15] At the same time, the victims were known to be chronic methadone users, which probably raised their tolerance to this substance. The published therapeutic and lethal concentrations for a number of substances may overlap and the diagnosis of intoxication cannot be made on the basis of toxicological analyses alone.[27,30] Karch and Stephens demonstrated that the presence of methadone is often an incidental finding during post-mortem examination which is unrelated to the cause of death and that post-mortem measurements of methadone or its metabolite cannot be used in isolation to identify which deaths are associated with methadone toxicity.[31] In all of the cases presented here, hair analysis confirmed repetitive cocaine use in all of the cases, but only in one case did the measured cocaine concentrations reached potentially lethal levels. In three cases, cocaine was not detectable in the blood samples. In two cases, benzoylecgonine was detected with blood concentration below its lethal level. This finding is not surprising if one takes into account the post-mortem redistribution phenomenon described by several authors.[32,33] Indeed, it is not possible to establish with certainty that a concentration of a given xenobiotic in samples taken post-mortem corresponds to the concentration at the time of death. This uncertainty also applies to cocaine.[32,33] In addition, the interpretation of death cases linked to cocaine consumption has been the topic of many debates for years. Thus, according to Karch, cocaine-associated sudden death is not dose-related and the relationship between cocaine blood concentrations and toxicity has not been established[34] This author suggested that except in very rare cases of massive overdose, cocaine-associated deaths occur only in long-term chronic users as chronic use leads to the formation of anatomical and neurochemical substrates that favor cardiovascular toxicity and sudden death. It was proposed[34,35] to consider cocaine as a cause of death in the presence of a strong history of cocaine abuse with typical myocardial pathology, even in face of a negative toxicology.

It is our opinion that in the cases presented here, chronic cocaine intoxication can indeed be considered as the cause of death. This view is compatible with the recommendations about the interpretation of deaths linked to cocaine use.[34,35,35] Clearly, the lesions we observed may constitute a morphological substrate for sudden death and they may well have been the result of chronic cocaine use. However, more studies, especially with controls, are needed.

Acknowledgement

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References

1. Chakko S, Myerburg RJ. Cardiac complications of cocaine abuse. *Clin Cardiol* 1995;**18**(2):67–72.
2. Dressler FA, Malekzadeh S, Roberts WC. Quantitative analysis of amounts of coronary arterial narrowing in cocaine addicts. *Am J Cardiol* 1990;**65**(5):303–8.
3. Fineschi V, Wetli CV, Di PM, Baroldi G. Myocardial necrosis and cocaine. A quantitative morphologic study in 26 cocaine-associated deaths. *Int J Legal Med* 1997;**110**(4):193–8.
4. Karch SB, Green GS, Young S. Myocardial hypertrophy and coronary artery disease in male cocaine users. *J Forensic Sci* 1995;**40**(4):591–5.
5. Karch SB, Billingham ME. Coronary artery and peripheral vascular disease in cocaine users. *Coronary Artery Dis* 1995;**6**(3):220–5.
6. Kloner RA, Hale S, Alker K, Rezkalla S. The effects of acute and chronic cocaine use on the heart. *Circulation* 1992;**85**(2):407–19.
7. Kloner RA, Rezkalla SH. Cocaine and the heart. *New Engl J Med* 2003;**348**(6):487–8 [comment].
8. Knuepfer MM. Cardiovascular disorders associated with cocaine use: myths and truths. *Pharmacol Therap* 2003;**97**(3):181–222.
9. Kringsholm B, Christoffersen P. Lung and heart pathology in fatal drug addiction. A consecutive autopsy study. *Forensic Sci Int* 1987;**34**(1–2):39–51.
10. Rajs J, Falconer B. Cardiac lesions in intravenous drug addicts. *Forensic Sci Int* 1979;**13**(3):193–209.

11. Rezkalla SH, Hale S, Kloner RA. Cocaine-induced heart diseases. *Am Heart J* 1990;**120**(6 Pt 1):1403–8.
12. Rump AF, Theisohn M, Klaus W. The pathophysiology of cocaine cardiotoxicity. *Forensic Sci Int* 1995;**71**(2):103–15.
13. Virmani R, Robinowitz M, Smialek JE, Smyth DF. Cardiovascular effects of cocaine: an autopsy study of 40 patients. *Am Heart J* 1988;**115**(5):1068–76 [see comment].
14. Michaud K, Romain N, Taroni F, Horisberger B, Mangin P. Evaluation of a simplified method of the conduction system analysis in 110 forensic cases. *Forensic Sci Int* 2002;**130**(1):13–24.
15. Winek CL, Wahba WW, Winek Jr CL, Balzer TW. Drug and chemical blood-level data 2001. *Forensic Sci Int* 2001;**122**(2–3):107–23.
16. Kitzman DW, Scholz DG, Hagen PT, Ilstrup DM, Edwards WD. Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity): a quantitative anatomic study of 765 specimens from subjects 20 to 99 years old. *Mayo Clin Proc* 1988;**63**(2):137–46.
17. Scholz DG, Kitzman DW, Hagen PT, Ilstrup DM, Edwards WD. Age-related changes in normal human hearts during the first 10 decades of life. Part I (Growth): A quantitative anatomic study of 200 specimens from subjects from birth to 19 years old. *Mayo Clinic Proc* 1988;**63**(2):126–36 [erratum appears in Mayo Clin Proc 1988 Jun;63(6):637].
18. James TN. Normal variations and pathologic changes in structure of the cardiac conduction system and their functional significance. *J Am Coll Cardiol* 1985;**5**(6 Suppl.): 71B–8B.
19. Lev M, Bharati S. Lesions of the conduction system and their functional significance. *Pathol Ann* 1974;**9**(0):157–207.
20. Cohle SD, Lie JT. Histopathologic spectrum of the cardiac conducting tissue in traumatic and noncardiac sudden death patients under 30 years of age: an analysis of 100 cases. *Anat Pathol* 1998;**3**:53–76.
21. Bauman JL, Grawe JJ, Winecoff AP, Hariman RJ. Cocaine-related sudden cardiac death: a hypothesis correlating basic science and clinical observations. *J Clin Pharmacol* 1994;**34**(9):902–11.
22. Krantz MJ, Rowan SB, Mehler PS. Cocaine-related torsade de pointes in a methadone maintenance patient. *J Addict Dis* 2005;**24**(1):53–60.
23. Ortega-Carnicer J, Bertos-Polo J, Gutierrez-Tirado C. Aborted sudden death, transient Brugada pattern, and wide QRS dysrrhythmias after massive cocaine ingestion. *J Electrocardiol* 2001;**34**(4):345–9.
24. Baughman KL. Diagnosis of Myocarditis: Death of Dallas Criteria. *Circulation* 2006;**113**(4):593–5.
25. Dettmeyer R, Baasner A, Schlamann M, Padosch SA, Haag C, Kandolf R, et al. Role of virus-induced myocardial affections in sudden infant death syndrome: a prospective postmortem study. *Pediatr Res* 2004;**55**(6):947–52.
26. Kuhl U, Pauschinger M, Bock T, Klingel K, Schwimmbeck CPL, Seeberg B, et al. Parvovirus B19 infection mimicking acute myocardial infarction. *Circulation* 2003;**108**(8):945–50.
27. Clark JC, Milroy CM, Forrest ARW. Deaths from methadone use. *J Clin Forensic Med* 1995;**2**(3):143–4.
28. Kornick CA, Kilborn MJ, Santiago-Palma J, Schulman G, Thaler DL, Keefe DL, et al. QTc interval prolongation associated with intravenous methadone. *Pain* 2003;**105**(3):499–506.
29. Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH. Effects of methadone on QT-interval dispersion. *Pharmacotherapy* 2005;**25**(11):1523–9.
30. Drummer O, Forrest AR, Goldberger B, Karch SB. Forensic science in the dock. *BMJ* 2004;**329**(7467):636–7.
31. Karch SB, Stephens BG. Toxicology and pathology of deaths related to methadone: retrospective review. *Western J Med* 2000;**172**(1):11–4 [see comment].
32. Drummer OH. Postmortem toxicology of drugs of abuse. *Forensic Sci Int* 2004;**142**(2–3):101–13.
33. Pounder DJ. The nightmare of postmortem drug changes. *Legal Med* 1993;163–91.
34. Karch SB, Stephens BS. When is cocaine the cause of death? *Am J Forensic Med Pathol* 1991;**12**(1):1–2.
35. Stephens BG, Jentzen JM, Karch S, Mash DC, Wetli CV. Criteria for the interpretation of cocaine levels in human biological samples and their relation to the cause of death. *Am J Forensic Med Pathol* 2004;**25**(1):1–10.